elevated amount of a molecule. Claim 1 has also been amended to emphasize that the patient has a particular HLA class I molecule that presents the molecule and that the individual (not the patient) from which the cytotoxic T lymphocytes are derived does not carry the particular HLA class I molecule presenting the molecule in the patient. This amendment finds support at least on page 3, lines 16 to 18, which makes it clear that the CTL are generated against selected peptides and therefore are specific. Similarly, page 3, lines 24 and 25, make it clear that the CTL can be made using the method of the third aspect of the invention, and page 13, lines 7 to 9, make it clear that the CTL made by this method is reactive against a selected molecule. In addition, it is clear from page 6, lines 3 to 7, that it is a *particular* HLA Class I molecule which presents the abnormal molecule ("... which individual does not carry *the* HLA Class I ... molecule type which, in the patient, presents at least part of said abnormal molecule ..." (emphasis added)). Claim 5 was amended to correct a typographical error. A copy of all of the pending claims as they are believed to have been amended is attached to this Amendment as an appendix.

The present invention is a method of treating a patient with diseased cells where the diseased cells contain an abnormal molecule, are associated with an abnormal molecule, contain an abnormally elevated amount of a molecule, or are associated with an abnormally elevated amount of a molecule. The patient is treated by administering cytotoxic T lymphocytes (CTL) to the patient. The CTL which is administered to the patient has to (1) recognize a particular molecule associated with the diseased cells presented by a particular HLA Class I molecule type, and (2) be derived from an individual who does not carry the HLA Class I molecule type which presents the particular molecule in the patient. In other words, it is not sufficient for there to be general HLA Class I mismatch between the recipient and the donor, there has to be mismatch

with respect to the particular HLA Class I molecule which presents the particular molecule associated with the diseased cells. Thus, the claimed method is one which exploits HLA-mismatch and makes the response against a particular allogeneic MHC molecule peptide specific. Claim 1 has been amended to clarify this specific relationship.

Unity of Invention

Applicant disagrees with the comments concerning lack of unity and Yin *et al*. The unifying concept, which is not disclosed or suggested by the prior art, is the selection, for use in therapy, of a CTL which recognizes a particular molecule which is presented by a particular HLA Class I type molecule which, in the intended recipient, presents the particular molecule. Yin *et al* relates to a superantigen-like molecule which is presented by various MHC Class I molecules including self MHC molecules (and not by a particular allogeneic MHC Class I molecule), and so does not disclose or suggest this concept. Since there is a unifying concept not disclosed in the prior art, the present holding of lack of unity is improper. Accordingly, applicant respectfully requests rejoinder and examination of claims 20-43 and 45-49.

Sequence Rules

As requested, applicant encloses with this Amendment a 3 & 1/2" diskette containing a computer-readable form of the Sequence Listing as well as a paper copy of the Sequence Listing.

Declaration under 37 C.F.R. § 1.821(f)

I declare that the material on the diskette is identical to the enclosed paper copy of the Sequence Listing and the sequences as filed in the application on August 7, 1998, that the Sequence Listing does not add new matter to the application, and that all statements made on information and belief are believed to be true and further that these statements were made with

the knowledge that willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Abstract

As requested, applicant submits with this Amendment an abstract of the disclosure on a separate page (page 72). Applicant notes that the wording of the abstract is identical to the abstract of the parent PCT application.

Declaration

The declaration was objected to as incorrectly claiming priority to the parent PCT application PCT/GB97/00118 under 35 U.S.C. § 119(a-d). A new oath was required.[1] Applicant disagrees that the originally filed declaration is improper. Applicant believes that it is proper to claim priority in a national stage application to the parent PCT application under 35 U.S.C. § 365(a). Since the parent PCT application is listed in the declaration in the section that covers claims to priority under 35 U.S.C. § 365(a), it is believed that the originally filed declaration is proper.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 1-9 and 14-18 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

1. Claim 5 was objected to as containing a typographical error. In response, applicant has amended claim 5 to replace "mutuant" with "mutant."

[1] Applicant assumes that if the requirement was valid a new declaration would also be responsive since the rules allow applicant to file either an oath or declaration.

2. Claim 1 was considered indefinite in the recitation "diseased cells which cells contain, or are associated with, an abnormal molecule or abnormally elevated amount of a molecule." Applicant first asserts that the meaning of this phrase is sufficiently clear, referring to (1) diseased cells that contain an abnormal molecule, (2) diseased cells that are associated with an abnormal molecule, (3) diseased cells that contain an abnormally elevated amount of a molecule, or (4) diseased cells that are associated with an abnormally elevated amount of a molecule. The phrase recited in the claim is merely are more concise recitation. Applicant specifically notes that the "molecule" that is at an abnormally elevated level need not be an abnormal molecule. It can be a normal molecule. In this case, it is the level of the molecule that is abnormal. Applicant asserts that the language of the claim does not specify whether this molecule is abnormal of not and thus the claim encompasses both possibilities.

Applicant further notes that the phrase "diseased cells which cells contain, or are associated with, an abnormal molecule or abnormally elevated amount of a molecule" is clear to the person skilled in the art when considering it in the context of the claimed invention. In relation to the claimed method, the skilled person may be considered to be a diagnostician such as a physician or clinical biochemist. Such skilled persons routinely determine whether a cell, for example in a tissue sample, is a diseased cell which contains or is associated with an abnormal molecule, or whether the diseased cell has an abnormally elevated amount of a molecule. That is their job.

Notwithstanding this, claim 1 has been amended to clarify that the cells of the patient either contain, or are associated with, an abnormal molecule or contain, **or** are associated with, an abnormally elevated amount of a molecule.

3. Claim 1 was also considered indefinite in the recitation "abnormal molecule." The term "abnormal molecule" is not limited to a molecule containing a mutation, but it *includes* such molecules. This is clear from the specification where, on page 6, lines 21 to 24, a preference for mutant polypeptides are given, whereas on page 9, lines 16 and 17, it is clear that abnormal glycosylation (which may not be due to mutation) is included. The term also includes molecules that are expressed in a transformed or virus-infected cell but are not expressed in a normal cell, and it includes cells expressing tumor antigens and viral antigens. Thus, a molecule can be an abnormal form of a normal molecule or a molecule abnormal in its presence in cells. Both forms are encompassed by the claims.

4. Claim 1 was also considered indefinite in the recitation of "HLA class I (or equivalent) molecule." As defined from page 3, line 27, to page 4, line 4, this term refers to "any protein which is equivalent to a human HLA class I molecule from any other animal." The specification provides the mouse MHC class I proteins as examples of equivalent molecules.

Rejection Under 35 U.S.C. § 102

Claims 1-9 were rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,928,639 to Slavin et al. as evidenced by Wu et al., *J. Biol. Chem.* 270:5944 (1995). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

1. In the claimed method, the CTL which is administered to the patient has to (1) recognize a *particular* molecule associated with the diseased cells presented by a particular HLA Class I molecule type, and (2) be derived from an individual who does *not* carry the HLA Class I molecule type which presents the *particular* molecule *in the patient*. In other words, it is not

sufficient for there to be *general* HLA Class I mismatch between the recipient and the donor, there has to be mismatch with respect to the *particular* HLA Class I molecule which presents the *particular* molecule associated with the diseased cells. Thus, the claimed method is one which exploits HLA-mismatch and makes the response against a particular allogeneic MHC molecule *peptide specific*. Applicant asserts that the cited prior art cited fails to disclose or suggest these requirements. Furthermore, applicant submits that there was a prejudice in the art against the approach.

2. Slavin discloses a method for treating leukemia by administering non-specific allogeneic CTL from an individual fully HLA compatible with the patient. Slavin fails to disclose the use of CTL specific for tumor-associated antigens as required by the claims. Slavin also fails to disclose using CTL from an individual who does not carry the HLA Class I molecule type which in the patient presents the tumor antigen as required by the claims. The Slavin approach is based on allo-reactivity *without peptide specificity*. In fact, Slavin in general and for preference proposes the use of *HLA-compatible* allogeneic lymphocytes (see column 1, lines 15 to 20 and throughout the patent), presumably to limit uncontrollable reactions against allogeneic HLA molecules. It is quite clear from Slavin that *fully* HLA-compatible cells are much preferred, although some mismatch may be *tolerated* if fully matched cells are not available (see, for example, column 5, lines 45 to 56 and column 9, lines 41 to 50).

There is no disclosure in Slavin of which antigens the CTLs are recognizing. In fact, there is no disclosure of any specific tumor-associated antigens at all, let alone any suggestion that CTL administered to the patient should be specific for the tumor antigen. Furthermore, there is absolutely nothing in Slavin which would suggest using CTL from an individual who does not

carry the HLA Class I molecule type *which presents the tumor antigen* in the patient. To the contrary, Slavin very strongly suggests that the donor should be *fully* HLA compatible and it is only if fully compatible donors are not available that mismatch donors may be *tolerated.*

The method of the present application, unlike Slavin uses allogeneic, HLA-mismatched lymphocytes *specific* for selected molecules, such as peptide epitopes, expressed in diseased cells. The selected molecules are presented by particular HLA Class I molecules. When the method is applied to leukemic cells, as specifically described in the application, CTL are generated with GVL activity but no GVHD activity. This is very different from the Slavin approach which is based on allo-reactivity *without* peptide specificity.

With reference to the particular passages in Slavin referred to in the Office Action, there is no disclosure of a peptide-specific response. Column 13, lines 40 to 59, says nothing about the tumor antigen. In addition, the cited experiments with BALB/c mice injected with allogeneic C57 lymphocytes are misleading. Although they demonstrate a graft versus leukemia (GVL) effect, the experimental system does not measure graft versus host disease (GVHD). The killing of BCL1 leukemic cells (GVL) is measured in a secondary healthy recipient. The mice that were actually treated with the C57 lymphocytes presumably developed severe GVHD, which under the conditions used would not transfer to the secondary recipients wrongly giving the impression that GVL occurred without severe GVHD. Similarly, column 18, lines 36-55, column 19, lines 1-19, and Claims 1, 2 and 14 of Slavin are *silent* about the tumor antigens.

There is nothing in Slavin which suggests making the allogeneic response specific for selected target antigens, such as WT-1 and GATA-1 reported by Wu *et al.*

To summarize, Slavin fails to disclose the use of CTL specific for tumor-associated antigens and fails to disclose using CTL from an individual who does not carry the HLA Class I molecule type which in the patient presents the tumor antigen. Since both these features are required by the claims, Slavin fails to disclose every aspect of the claimed method. Accordingly, the claims are novel over Slavin.

Rejection Under 35 U.S.C. § 103

Claims 1-9 and 14-18 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Kohler et al., *Cancer Immunol. Immunother*. 26:74 (1988), or U.S. Patent No. 5,994,523 to Kawakami et al., in view of Yin et al., *Eur. J. Immunol*. 24:1990 (1988), or Huang et al., *Cancer Immunol. Immunother*. 38:399 (1994), and U.S. Patent No. 5,928,639 to Slavin et al., or Wu et al., *J. Biol. Chem*. 270:5944 (1995). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

1. The claimed method requires the use of CTL specific for tumor-associated antigens and the use of CTL from an individual who does not carry the HLA Class I molecule type which presents the tumor antigen in the patient.

2. Slavin was discussed above. The Slavin protocol recognizes numerous allogeneic minor and major histocompatibility antigens of the host. It is impossible to know which of these histocompatibility antigens are expressed on host normal tissues or malignant tissues or both. Thus, in the Slavin work, it is impossible to dissect graft versus host disease (GVHD) from graft versus leukemia (GVL). The Slavin approach is fundamentally the same as donor lymphocyte infusion (DLI) therapy that is currently used for treatment of leukemia, with the exception that Slavin proposes the infusion of lymphocytes from an allogeneic donor after autologous bone

marrow transplantation, whereas DLI is done after allogeneic transplantation using lymphocytes from the same allogeneic donor. Since 1990 the major problem of DLI has remained GVHD, and various research groups are still trying to develop methods to dissociate it from GVL.

The work by Kohler *et al.* is again a version of the DLI therapy. It is quite clear that the allogeneic CTL are *HLA-haploidentical* and that this is an important part of the procedure (see "Patient and Donor Selection" on page 75 from which it is clear that stringent steps were taken to establish HLA haplo identity). In this case the patients were not conditioned by bone marrow transplantation but by the treatment with cyclophosphamide. Again, there are no clues that would provide any information as to how the treatment could be made *antigen-specific* and how GVL and GVHD could be separated.

The protocol described by Kawakami *et al* is applicable to conventional self-HLA-restricted CTL responses. It would not work against proteins to which self-restricted CTL are tolerant and it provides no clues how to make allogeneic T cell responses antigen-specific. In particular, it is clear from column 36, line 60 *et seq* that the patient (patient number 1200) is treated with a TIL (TIL 1200) derived from his own tumor. Hence, the lymphocytes are fully HLA matched.

The experiments by Yin *et al.* describe CTL specific for a RAS-peptide that is presented in a superantigen-like fashion by various MHC (HLA) alleles including self MHC molecules. Superantigen-like recognition mechanisms do not provide any clue how to make allogeneic T cell responses specific for a peptide presented in the groove of an allogeneic MHC (HLA) molecule. In particular, the RAS peptide, as a superantigen, does not bind to a *particular* MHC

(HLA) molecule, but rather is "promiscuous" and binds to many *different* MHC HLA molecules). This is quite different from the present method.

Huang *et al* describe "non-fastidious CTL" that can recognize melanoma cells not expressing the MHC (HLA) molecules of the CTL. These CTL kill melanoma cells that do not share any HLA Class I alleles. The CTL recognized antigen(s) and the CTL restriction molecules are unknown in this system. In particular, as can be seen in Table 3 of Huang *et al*, the non-fastidious CTL are not selective for the particular antigen (whatever the antigen is in Huang *et al*) being presented by a *particular* HLA Class I molecule. This is in contrast to the present method where the CTL is selective for a particular molecule (such as a peptide) presented by a particular HLA Class I molecule. In other words, the CTL of the claimed method are peptide-specific and MHC restricted. Thus, the Huang experiments do not provide any clue how to make allogeneic T cell responses specific for defined peptide epitopes presented by a defined HLA allele.

The cited publications all fail to disclose or suggest, either alone or in combination, the use of CTL specific for tumor-associated antigens and the use of CTL from an individual who does not carry the HLA Class I molecule type which in the patient presents the tumor antigen. In fact, the cited publications teach away from the use of such CTL. Accordingly, the claimed method is not obvious in view of the cited publications.

3. The rejection asserts that "one with ordinary skill in the art would be motivated to make CTL specific for leukemia cells using the techniques taught by the prior art and to select CTL which are specific for leukemia cells but are capable of lysing allogeneic (HLA mismatched) leukemia cells using the methods taught by Yin *et al.* or Huang *et al.*" As noted above, neither

Yin *et al.* or Huang *et al.* teach CTL which are selective for a particular molecule (for example, a peptide) presented by a particular HLA Class I molecule. None of the other publications cure this deficiency. Thus, for at least this reason, the claimed method is not obvious from the cited publications. The cited publications simply fail to disclose or suggest what applicant is claiming. In particular, as noted above, Yin *et al.* provides no clue how to make allogeneic T cell responses specific for a peptide, and Huang *et al.* provides no clue how to make allogeneic T cell responses specific for a defined molecule presented by a defined HLA allele. It appears that the rejection is based on impermissible hindsight reconstruction of the claimed method.

In addition, the present method cannot obvious in view of the cited publication since the art of immunology stresses the fact that thymic education positively selects T cells that are self-MHC restricted; that is, such T cells efficiently recognize particular peptide antigens presented by self, but not allogeneic, MHC molecules. Thus, the claimed method goes against a fundamental immunological concept. Put another way, the claimed method is based on effects unexpected from the field of immunology. For this additional reason the claims are not obvious in view of the cited publications.

Allowance of claims 1-18, 20-43, and 45-49 is respectfully solicited.

Respectfully submitted,

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Date: July 19, 2000

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I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Teresa R. Spratt

Date: July 19, 2000

Appendix: Claims As Pending After Amendment

1. (Twice amended) A method of treating a patient with a disease wherein the patient contains diseased cells which cells contain, or are associated with, an abnormal molecule or an abnormally elevated amount of a molecule and which cells are capable of presenting at least part of the molecule on their surface by [an] a particular HLA class I (or equivalent) molecule, the method comprising administering to the patient a therapeutically effective amount of cytotoxic T lymphocytes (CTL) which are selected to specifically recognize at least part of the molecule when presented by an HLA class I (or equivalent) molecule on the surface of a cell characterised in that the cytotoxic T lymphocytes are derived from an individual which individual does not carry the HLA class I (or equivalent) molecule type which, in the patient, presents at least part of the abnormal molecule[, or molecule abnormally elevated,] contained in, or associated with, the diseased cells of the patient or presents an abnormally elevated of the molecule contained in, or associated with, the diseased cells of the patient.

2. (Unamended) A method according to Claim 1 wherein the CTL are a clonal population of CTL.

3. (Amended) A method according to Claim 1 wherein the CTL are substantially free of other cell types.

4. (Amended) A method according to Claim 1 wherein the molecule is a polypeptide.

5. (Twice amended) A method according to Claim 4 wherein the polypeptide is a [mutuant] mutant polypeptide associated with the diseased cells.

6. (Amended) A method according to Claim 4 wherein the polypeptide is present at a higher level in the diseased cells compared to non-diseased cells.

7. (Amended) A method according to Claim 1 wherein the disease is a cancer.

8. (Unamended) A method according to Claim 7 wherein the cancer is any one of breast cancer; bladder cancer; lung cancer; prostrate cancer; thyroid cancer; leukaemias and lymphomas such as CML, ALL, AML, PML; colon cancer; glioma; seminoma; liver cancer; pancreatic cancer; bladder cancer; renal cancer; cervical cancer; testicular cancer; head and neck cancer; ovarian cancer; neuroblastoma and melanoma.

9. (Amended) A method according to Claim 1 wherein the disease is caused by a chronic viral infection.

10. (Unamended) A method according to Claim 9 wherein the virus is any one of HIV, papilloma virus, Epstein-Barr virus, HTLV-1, hepatitis B virus, hepatitis C virus and herpes virus.

11. (Unamended) A method according to Claim 10 wherein the virus is HIV.

12. (Amended) A method according to Claim 1 wherein the disease is associated with an abnormally elevated amount of a hormone.

13. (Amended) A method according to Claim 1 wherein the disease is a bacterial disease caused by a chronic bacterial infection.

14. (Amended) A method according to Claim 1 further comprising the step of determining the HLA class I (or equivalent) molecule type of the patient prior to administration of the CTL.

15. (Amended) A method according to Claim 14 wherein the type is determined using DNA typing.

16. (Amended) A method according to Claim 1 wherein the patient is human.

17. (Amended) A method according to Claim 14 wherein the cytotoxic T lymphocyte is selected from a library of CTL clones, the library comprising a plurality of CTL clones derived from individuals with differing HLA class I (or equivalent) molecule type and each CTL clone recognises the diseased cells.

18. (Amended) A method according to Claim 17 wherein each CTL clone recognises at least part of the same molecule contained in or associated with the diseased cells.

20. (Amended) A method of making a clonal population of cytotoxic T lymphocytes (CTL) reactive against a selected molecule the method comprising the step of (a) co-culturing a sample containing CTL or a precursor thereof derived from a healthy individual with a stimulator cell which expresses HLA class I (or equivalent) molecules on its surface and that represents at least a part of the selected molecule in a large proportion of occupied HLA class I (or equivalent) molecules present on the surface of the stimulator cell and (b) selecting a CTL clone reactive against the selected molecule when at least a part of the molecule is presented by an HLA class I

(or equivalent) molecule on the surface of a cell, wherein the healthy individual does not carry the HLA class I (or equivalent) molecule type which, on the stimulator cell, presents at least a part of the selected molecule.

21. (Amended) A method according to claim 20 wherein the sample containing CTL or a precursor thereof is PBMC.

22. (Amended) A method according to Claim 20 wherein the molecule is a polypeptide.

23. (Amended) A method according to Claim 20 wherein the selected molecule is an abnormal molecule associated with a diseased cell, or a molecule associated with a diseased cell wherein an abnormally elevated amount of the molecule is present in the diseased cell.

24. (Amended) A method according to Claim 23 wherein the selected molecule is a mutuant polypeptide associated with a diseased cell or a polypeptide present at a higher level in the diseased cell compared to a non-diseased cell.

25. (Amended) A method according to Claim 23 wherein the diseased cell is any one of a cancer cell, a virus-infected cell, a bacterium infected cell and a cell expressing an abnormally elevated amount of a hormone.

26. (Amended) A method according to Claim 20 wherein the healthy individual is a human.

27. (Amended) A method according to Claim 26 wherein the selected molecule is any one of cyclin D1, cyclin E, mdm 2, EGF-R, erb-B2, erb-B3, FGF-R, insulin-like growth factor receptor, Met, myc, p53, BCL-2, ie mutant Ras, mutant p53, a polypeptide associated with the BCR/ABL translocation in CML and ALL, mutant CSF-1 receptor, mutant APC, mutant RET, mutant EGFR, a polypeptide associated with PML/RARA translocation in PML, a polypeptide associated with E2A-PBX1 translocation in pre B leukaemias and in childhood acute leukaemias, human papilloma virus proteins, Epstein-Barr virus proteins, HTLV-1 proteins, hepatitis B or C virus proteins, herpes-like virus proteins and HIV encoded proteins.

28. (Amended) A method according to Claim 20 further comprising determining the HLA Class I (or equivalent) type of the healthy individual.

29. (Amended) A method according to Claim 28 wherein the HLA class I (or equivalent) type is determined by DNA analysis.

30. (Amended) A method according to Claim 20 wherein the stimulator cell has a type of HLA class I (or equivalent) molecule on its surface which HLA class I (or equivalent) molecule type is not present in the healthy individual.

31. (Amended) A method according to Claim 20 wherein the stimulator cell is a cell which is substantially incapable of loading the HLA class I (or equivalent) molecule with at least a part of the selected molecule.

32. (Amended) A method according to Claim 31 wherein the cell is a mammalian cell defective in the expression of a peptide transporter.

33. (Unamended) A method according to Claim 32 wherein the mammalian cell lacks or has a reduced level of the TAP peptide transporter.

34. (Amended) A method according to Claim 31 wherein the cell is an insect cell.

35. (Amended) A method according to Claim 34 wherein the cell is a *Drosophila* cell.

36. (Amended) A method according to Claim 20 wherein the stimulator cell is a host cell transfected with a nucleic acid molecule capable of expressing the HLA class I (or equivalent) molecule.

37. (Amended) A method according to Claim 36 wherein the host cell before transfection expresses substantially no HLA class I (or equivalent) molecules.

38. (Amended) A method according to Claim 20 wherein the stimulator cell expresses a molecule important for T cell costimulation.

39. (Unamended) A method according to Claim 38 wherein the molecule important for T cell costimulation is any of B7.1, B7.2, ICAM-1 and LFA3.

40. (Amended) A method according to Claim 20 wherein substantially all the HLA class I (or equivalent) molecules expressed on the surface of the stimulator cell are of the same type.

41. (Amended) A clonal population of cytotoxic T lymphocytes reactive against a selected molecule obtainable by the method of Claim 20.

42. (Unamended) A clonal population of cytotoxic T lymphocytes according to Claim 41 for use in medicine.

43. (Unamended) A pharmaceutical composition comprising a clonal population of cytotoxic T lymphocytes reactive against a selected molecule according to Claim 41 and a pharmaceutically acceptable carrier.

45. (Amended) A library of CTL clones, the library comprising a plurality of CTL clones derived from individuals and each CTL clone is restricted by a different HLA class I allele and recognises a molecule associated with a selected disease.

46. (Unamended) A therapeutic system comprising (a) means to determine the HLA class I (or equivalent) type of a patient to be treated and (b) a library of CTL clones as defined in Claim 45.

47. (Amended) A method of making a cytotoxic T lymphocyte (CTL) suitable for treating a patient, the method comprising making a clonal population of CTL by the method of Claim 20; preparing a genetic construct capable of expressing the T-cell receptor (TCR) of the clonal population of CTL, or a functionally equivalent molecule; and introducing the genetic construct into a CTL or precursor thereof which CTL or precursor is derived from the patient.

48. (Unamended) A cytotoxic T lymphocyte suitable for treating a patient obtainable by the method of Claim 47.

49. (Amended) A method of treating a patient with a disease wherein the patient contains diseased cells which cells contain, or are associated with, an abnormal molecule or an abnormally elevated amount of a molecule and which cells are capable of presenting at least part of the molecule on their surface by an HLA class I (or equivalent) molecule, the method comprising administering to the patient a therapeutically effective amount of cytotoxic T lymphocytes (CTL) which recognize at least part of the molecule when presented by an HLA class I (or equivalent) molecule on the surface of a cell wherein the CTL is a CTL according to Claim 48.